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WO 03/106403 A1

(54) Title: CARBOXAMIDES DERIVATIVES RCK 30

(57) Abstract: The present invention relates to carboxamides which are useful as an active ingredient of pharmaceutical preparations. The carboxamides of the present invention have IP receptor antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with IP receptor antagonistic activity.Such diseases include urological diseases or disorder as follows: bladder outlet obstruction, overactive bladder, urinary incontinence, detrusor hyper-reflexia, detrusor instability, reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benighn prostatic hypertrophy (BPH), prostatitis, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity.The compounds of the present invention are also useful for treatment of pain including, but not limited to inflammatory pain, neuropathic pain, acute pain, chronic pain, dental pain, premenstrual pain, visceral pain, headaches, and the like; hypotension;hemophilia and hemorrhage; and inflammation, since the diseases are alleviated by treatment with an IP receptor antagonist.

Carboxamides derivatives

Detailed Description of Invention

Technical Field

The present invention relates to a carboxamide derivatives which are useful as an active ingredient of pharmaceutical preparations. The carboxamides of the present invention have IP receptor antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with IP receptor antagonistic activity.

More specifically, the carboxamide derivatives of the present invention are useful for treatment and prophylaxis of urological diseases or disorders.

The compounds of the present invention are also useful for treatment of pain; hypotension; hemophilia and hemorrhage; inflammation; respiratory states from allegies or asthma, since the disease also is alleviated by treatment with an IP receptor antagonist.

BACKGROUND ART

Prostaglandins (or prostanoids, PGs) are a group of bioactive lipid mediators generated from membrane phospholipids. They are formed from 20-carbon essential fatty acids containing 3, 4, or 5 double bonds, and carry a cyclopentane ring. They are divided into 6 main classes (D, E, F, G, H or I) by the cyclopentane ring structure. The main classes are further subdivided by subscripts 1, 2, or 3, reflecting their fatty acid precursors. PGI2 is a member of prostanoids, and it has a double ring structure and is derived from arachidonic acid. The receptor for PGI2 is a seven transmembrane G-protein coupled receptor, called IP receptor. IP receptor couples at least to Gs-type G-protein, and activates adenylate cyclase and phospholipase C. The

678-682.). Injection of acetic acid into the peritoneal cavity induced production of PGI2. This PGI2 is considered to bind to IP receptor on sensory neurons. As IP receptor couples to the activation of both adenylate cyclase and phospholipase C, cAMP-dependent protein kinase (PKA) and protein kinase C (PKC) are activated. PKA and PKC are known to modulate ion channels on sensory neurons such as VR1, P2X3, and TTX-R. As a result, PGI2 sensitizes sensory neurons to enhance the release of neurotransmitters. Hence, acetic acid injection induces nociceptive response (writhing) in mice. This acetic acid-induced writhing was greatly reduced in IP receptor-null mice as the same level as indomethacin-treated wild type mice. Several other in vivo hyperalgesia studies in rodents and in vitro studies further support that PGI2 plays a major role in the induction of hyperalgesia and that PGI2 acts as important modulator of sensory neurons (K. Bley et al, Trends in Pharmacological Sciences 1998, 19(4), 141-147.). Therefore, IP receptor antagonists may be useful for the treatment of pain.

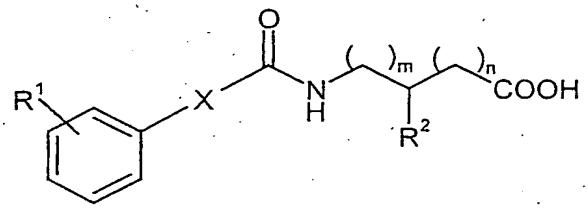
Sensory neurons play very important roles not only in the pain sensation but also in the sensation of bladder distension. In normal subjects, A-delta sensory fibers are considered to play a major role to sense the bladder distention. However, in disease conditions of overactive bladder by, but not limited to, spinal cord injury, cystitis, Parkinson's disease, multiple sclerosis, previous cerebrovascular accident, and bladder outlet obstruction (BOO) caused by benign prostate hyperplasia (BPH), the sensitivity of C-fiber sensory neurons is upregulated and they contribute to the induction of the lower urinary tract symptoms. Treatment of overactive bladder patients with intravesical injection of capsaicin or its potent analog, resiniferatoxin, both of which desensitize VR1-positive C-fiber afferent neurons innervating the bladder, has been shown to be efficacious in several clinical trials (C. Silva et al, Eur Urol. 2000, 38(4), 444-452.). Therefore, C-fiber sensory neurons play an important role in the pathology of overactive bladder. PGI2 is generated locally in the bladder and it is the major prostaglandin released from the human bladder. In a rabbit BOO model, a stable metabolite of PGI2 was reported to be increased in BOO bladder (JM. Masick et al, Prostaglandins Other Lipid Mediat. 2001, 66(3), 211-219.).

The development of a compound which has effective IP receptor antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with IP receptor antagonistic activity has been desired.

Summary of the invention

As the result of extensive studies on chemical modification of carboxamides derivatives, the present inventors have found that the compounds of the structure related to the present invention have unexpectedly excellent IP receptor antagonistic activity. The present invention has been accomplished based on these findings.

This invention is to provide a novel carboxamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

m and n independently represent an integer from 0 to 2;

-X- represents $-CH_2-CH_2-$, -CH=CH-, or -C≡C-;

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or

The compounds of the present invention surprisingly show excellent IP receptor antagonistic activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful for diseases, is alleviated by treatment with an IP receptor antagonist.

More specifically, since the carboxamides derivatives of the present invention antagonize IP receptor, they are useful for treatment and prophylaxis of urological diseases or disorder.

The compounds of the present invention are also useful for treatment of urological diseases or disorders. Such diseases or disorders include bladder outlet obstruction, overactive bladder, urinary incontinence, detrusor hyper-reflexia, detrusor instability, reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benighn prostatic hypertrophy (BPH), prostatitis, urinary frequency, nocturia, urinary urgency, pelvic hypersensitivity, urethritis, pelvic pain syndrome, prostatodynia, cystitis, or idiophatic bladder hypersensitivity.

The compounds of the present invention are also useful for treatment of pain including, but not limited to inflammatory pain, neuropathic pain, acute pain, chronic pain, dental pain, premenstrual pain, visceral pain, headaches, and the like; hypotension;hemophilia and hemorrhage; inflammation; respiratory states from allegies or asthma, since the diseases which are alleviated by treatment with IP receptor antagonist.

In another embodiment, the present invention provides a carboxamide derivative of the formula (I'), its tautomeric or stereoisomeric form, or a salt thereof:

R^{14} and R^{15} independently represent hydrogen, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, or (C_{1-6}) alkoxy optionally substituted by aryl or heteroaryl,

or

R^{14} and R^{15} together with the CH to which they are attached, form a (C_{3-8})cycloalkyl optionally interrupted by NH, or O, or a phenyl optionally substituted by hydroxy, halogen or (C_{1-6}) alkyl;

R^2 represents hydrogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by amino, (C_{1-6})alkylamino, or phenyl.

Yet another embodiment of the compounds of formula (I) or (I') are those wherein:

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{2-6})alkenyl substituted by aryl or heteroaryl, (C_{2-6})alkynyl substituted by aryl or heteroaryl, or (C_{1-6}) alkyl substituted by aryl or heteroaryl;

R^{12} and R^{13} independently represent (C_{2-6})alkenyl substituted by aryl or heteroaryl, (C_{2-6})alkynyl substituted by aryl or heteroaryl, or (C_{1-6}) alkyl substituted by aryl or heteroaryl;

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Aryl per se represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl and phenanthrenyl.

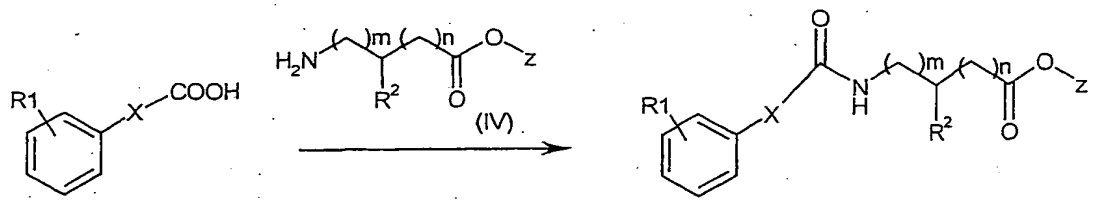
Heteroaryl per se represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Hetero ring (heterocyclyl) per se represents a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to 10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The reaction can be advantageously carried out in the presence of a base including, for instance, an alkali metal alkoxide such as sodium methoxide, sodium ethoxide and potassium tert-butoxide; alkali metal hydroxide such as sodium hydroxide, lithium hydroxide and potassium hydroxide; and others.



(III) (II)

The compound of formula (II) (wherein R^1, R^2, X, Z, m and n are the same as defined above) can be prepared by the reaction of compound (III) with amine (IV).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF)and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); ketones such as acetone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The reaction can be advantageously carried out in the presence of a base including, for instance, an alkali metal hydride such as sodium hydride or potassium hydride; alkali metal alkoxide such as sodium methoxide, sodium ethoxide and potassium tert-butoxide; alkali metal hydroxide such as sodium hydroxide and potassium hydroxide; alkali metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; alkaline earth metal alkoxides such as magnesium ethoxide; organic amines such as pyridine, triethylamine and N,N-diisopropyl-ethylamine, dimethylaniline, diethylaniline
and others.

The compound (V) or (V)' can be commercially available or can be prepared by either the use of the similar procedure for the preparation of the compound of formula (II) or known techniques. The compound (VI) or (VI)' can be commercially available or can be prepared by the use of known techniques.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

centrifugation and washed with binding assay buffer (BAB: 50 mM Tris-HCl, 5 mM $MgCl_2$ (pH 7.5)). Cells were suspended at the density of 6.25 x 10^6 cells/ml in BAB, and one million cells in 160 µl aliquot of cell suspension were put in a well of 96 well plate (Falcon). Then, 20 µl of compound solution, 100 µM of iloprost (for non-specific binding), or buffer alone (total binding), diluted with 1% DMSO in BAB was added. Finally, another 20 µl containing [^{3}H]-iloprost (0.02 µCi, 0.5-1 pmol) in BAB was added and incubated at room temperature for 30 min with a gentle shaking. Cell suspension was then transferred to a well of MultiScreen plate with GF/C glass filters (Millipore) to harvest cells. Cells were washed twice with 200 µl of ice-cold BAB and the plate was kept at 55°C for 30 min to dry filters. The filter in the well was punched out to a counting tube and 2 ml of Ultima Gold XR (Packard) was added. [^{3}H]-radio activity in the filter was measured by a liquid scintillation counter (Beckman).

[Iloprost-induced cAMP production assay in HEL cells] (Assay 2)

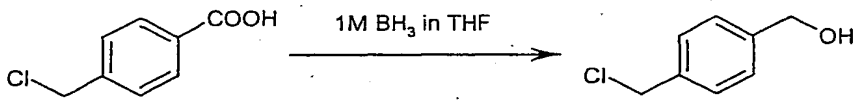
HEL cells were collected with centrifugation and washed with cAMP assay buffer (CAB: Hank's balanced salt solution, 17 mM Hepes, 0.1% bovine serum albumin, 1 mM IBMX, 0.4% DMSO, and 1 mM L-ascorbic acid sodium salt (pH 7.4)). Cells were suspended at the density of 2.5 x 10^5 cells/ml in CAB, and twenty thousand cells in 80 µl aliquot of cell suspension were put in a well of 96 well plate (Falcon). Then, 10 µl of compound solution diluted with 1% DMSO in CAB or buffer alone was added. The plate was incubated at 37°C for 30 min. Then, another 10 µl containing 100 nM iloprost in CAB or buffer alone was added and further incubated at 37°C for 30 min. cAMP content in the well was measured by a cAMP ELISA kit (Applied Biosystems).

IC50 = A 0.1μM < B 1 μM < C

The compounds of the present invention also show excellent selectivity, and strong activity in vivo assays.

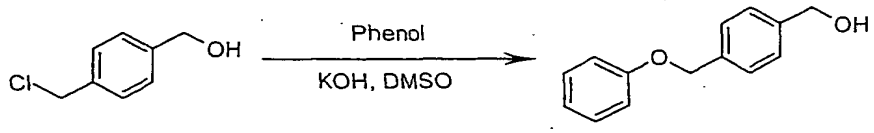
Example 1:

(1) 4-Chloromethylbenzyl Alcohol



To a solution of 4-chloro-4-toluic acid in tetrahydrofuran (THF, 60 ml) was added 1 M borane THF solution (90 ml). The mixture was stirred at room temperature overnight and quenched by addition of methanol (50 ml). The solvent was evaporated off and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 3/1) to obtain 4-chloromethylbenzyl Alcohol (8.84 g, 96%) as a colorless solid.

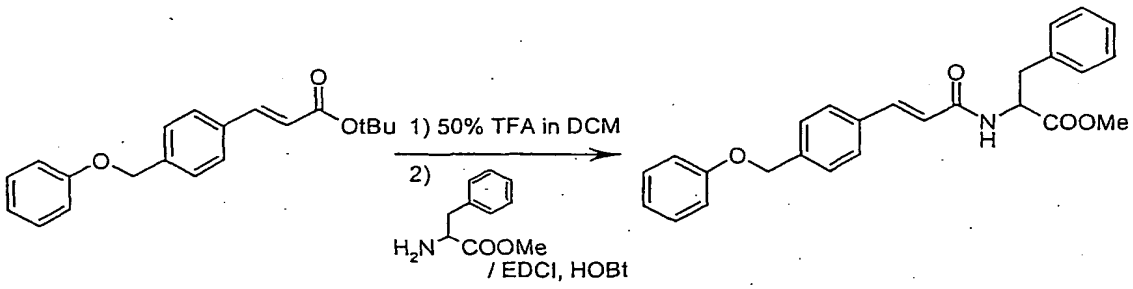
(2) 4-Phenoxymethylbenzyl Alcohol



A mixture of 4-chloromethylbenzyl alcohol (0.80 g), phenol (0.48 g), 85% potassium hydroxide (0.76 g) and dimethylsulfoxide (DMSO, 15 ml) was stirred at room temperature overnight and poured into a mixture of water (50 ml) and ethyl acetate (50 ml). The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed off and the residue was purified by silica gel column

gel column chromatography (hexane/ethyl acetate = 4/1) to obtain tert-butyl 4-phenoxymethylcinnamate (0.73 g, 100%) as a colorless solid.

(5) N-(4-Phenoxymethylcinnamoyl)phenylalanine Methyl Ester

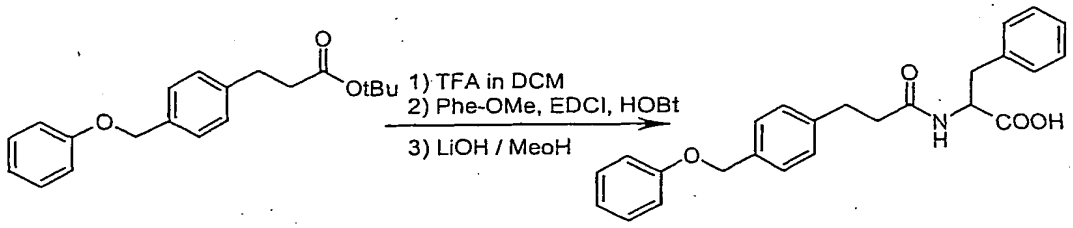


A mixture of tert-butyl 4-phenoxymethylcinnamate (0.20 g), trifluoroacetic acid (TFA, 1 ml) and dichloromethane (1 ml) was allowed to stand for 2.5 hr at room temperature. The solvent was removed in vacuo and the residue was dissolved in N,N-dimethylformamide (DMF, 5 ml). To the solution were added phenylalanine methyl ester (0.15 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 0.18 g), 1-hydroxybenzotriazole (HOBt, 0.12 g) and triethylamine (0.12 ml). The mixture was stirred at room temperature overnight and poured into a mixture of water (30 ml) and ethyl acetate (20 ml). The organic layer was washed with water and dried over sodium sulfate. The solvent was removed off and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain N-(4-phenoxymethylcinnamoyl)phenylalanine methyl ester (0.22 g, 88%) as a colorless solid.

(6) N-(4-phenoxymethylcinnamoyl)phenylalanine

To a mixture of tert-butyl 4-phenoxymethylcinnamate (see: example 1-(4), 0.20 g) and nickel chloride hexahydrate (0.02 g) in methanol (4 ml) was added sodium borontetrahydride (0.05 g) on an ice-water bath. The mixture was stirred at room temperature for 1 hr and quenched with saturated ammonium chloride water solution. The resulting suspension was extracted with ethyl acetate and the organic layer was washed with water and dried over sodium sulfate. The solvent was removed off and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to obtain tert-butyl 3-(4-phenoxymethylphenyl)propionate (0.168 g, 84%) as a colorless solid.

(2) N-[3-(4-Phenoxymethylphenyl)propionyl]phenylalanine



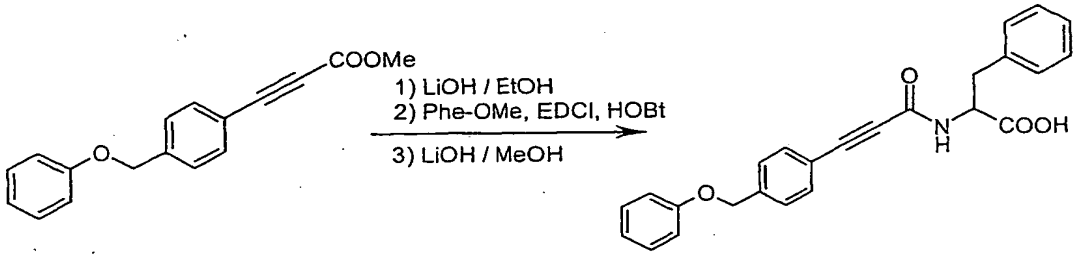
To a solution of tert-butyl 3-(4-phenoxymethylphenyl)propionate (0.10 g) in ethanol (2 ml) was added 1N lithium hydroxide water solution (0.7 ml). The mixture was stirred at 60°C for 3 hr and concentrated in vacuo. The residue was suspended in a mixture of 1N hydrochloric acid (0.7 ml), water (5 ml) and ethyl acetate (10 ml) and the organic layer was washed with brine and dried over sodium sulfate. The solvent was removed off and the residue was used for the following steps towards N-[3-(4-Phenoxymethylphenyl)propionyl]phenylalanine, according to the procedures for the synthesis of N-(4-phenoxymethylcinnamoyl)phenylalanine (See: example 1-(5) and (6)).

mp 173-174 °C; Calcd [M+1]: 404, Found: m/z 404.

Molecular weight: 403.48

To a solution of 1-iodo-4-(phenoxymethyl)benzene (0.40 g) and methyl propiolate (0.43 g) in THF (8 ml) were added Biskis(triphenylphosphine)palladium dichloride (18 mg), cuprous iodide (10 mg) and potassium carbonate (0.36 g). The mixture was stirred at 80°C and consentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to obtain methyl 4-phenoxymethylphenylpropiolate (0.155 g, 45%) as colorless flakes.

(3) N-(4-Phenoxymethylphenylpropioloyl)phenylalanine



According to the procedure for the synthesis of N-(4-phenoxymethylcinnamoyl)phenylalanine (See: example 1-(5) and (6)) from tert-butyl 4-phenoxymethylcinnamate, N-(4-phenoxymethylphenylpropioloyl)phenylalanine was prepared from 4-phenoxymethylphenylpropiolic acid, which was obtained from the corresponding methyl ester by the hydrolysis with 1N lithium hydroxide in ethanol.

mp 146 °C; Calcd [M+1]: 400, Found: m/z 400.

Molecular weight: 399.44

Activity grade assay 2: A

^{1}H-NMR (500 MHz, DMSO-*d6*): δ 2.92 (1H, dd, J = 13.8, 10.1 Hz), 3.13 (1H, d, J = 13.9, 4.7 Hz), 4.46-4.51 (1H, m), 5.16 (2H, s), 6.95 (1H, t, J = 7.3 Hz), 7.01 (2H, d, J = 7.9 Hz), 7.20-7.31 (6H, m), 7.52 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 9.14 (1H, d, J = 8.2 Hz), 12.88 (1H, bs).

obtain N-(4-benzyloxycinnamoyl)phenylalanine, according to the procedure for the synthesis of N-(4-phenoxymethylcinnamoyl)phenylalanine (See: example 1-(6)).

mp 220 °C; Calcd [M+1]: 402, Found: m/z 402.

Molecular weight: 401.46

Activity grade assay 2: A

^{1}H-NMR (500 MHz, DMSO-*d6*): δ 2.92 (1H, dd, J = 9.5, 13.9 Hz), 3.11 (1H, dd, J = 5.1, 14.2 Hz), 4.55 (1H, m), 5.14 (2H, s), 6.55 (1H, d, J = 15.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.18-7.21 (1H, m), 7.23-7.35 (6H, m), 7.38-7.41 (1H, m), 7.44-7.46 (1H, m), 7.49 (2H, d, J = 8.9 Hz), 12.77 (1H, br s).

or

R^{12} and R^{13} together with the nitrogen atom to which they are attached, form a 5-7 membered saturated hetero ring optionally interrupted by O or NH;

R^{14} and R^{15} independently represent hydrogen, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, or (C_{1-6}) alkoxy optionally substituted by aryl or heteroaryl,

or

R^{14} and R^{15} together with the CH to which they are attached, form a (C_{3-8})cycloalkyl optionally interrupted by NH, or O, or a phenyl optionally substituted by hydroxy, halogen or (C_{1-6}) alkyl; and

R^2 represents hydrogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by amino, (C_{1-6})alkylamino, or phenyl.

2. A carboxamide derivative of the formula (I'), its tautomeric or stereoisomeric form, or a salt thereof:

R^{14} and R^{15} independently represent hydrogen, (C_{2-6})alkenyl optionally substituted by aryl or heteroaryl, (C_{2-6})alkynyl optionally substituted by aryl or heteroaryl, (C_{1-6}) alkyl optionally substituted by aryl or heteroaryl, or (C_{1-6}) alkoxy optionally substituted by aryl or heteroaryl,

or

R^{14} and R^{15} together with the CH to which they are attached, form a (C_{3-8})cycloalkyl optionally interrupted by NH, or O, or a phenyl optionally substituted by hydroxy, halogen or (C_{1-6}) alkyl; and

R^2 represents hydrogen, cyano, (C_{1-6}) alkoxy, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-7})cycloalkyl, or (C_{1-6}) alkyl optionally substituted by amino, (C_{1-6})alkylamino, or phenyl.

3. The carboxamide derivative, its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 or 2,

wherein

R^1 represents $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-NR^{12}R^{13}$, or $-CHR^{14}R^{15}$,

wherein

R^{11} represents (C_{2-6})alkenyl substituted by aryl or heteroaryl, (C_{2-6})alkynyl substituted by aryl or heteroaryl, or (C_{1-6}) alkyl substituted by aryl or heteroaryl;

R^2 is benzyl.

7. The carboxamide derivative, its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said derivative is selected from the group consisting of the following compounds:

N-(4-phenoxymethylcinnamoyl)phenylalanine;
N-[3-(4-Phenoxymethylphenyl)propionyl]phenylalanine;
N-(4-Phenoxymethylphenylpropioloyl)phenylalanine; and
N-(4-Benzyloxycinnamoyl)phenylalanine.

8. A medicament comprising the carboxamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 or 2 as an active ingredient.

9. The medicament as claimed in claim 8, further comprising one or more pharmaceutically acceptable excipients.

10. The medicament as claimed in claim 8, wherein the carboxamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is an IP receptor antagonist.

11. The medicament as claimed in claim 8 for prophylaxis and/or treatment of urological disorder or disease.

12. The medicament as claimed in claim 8 for prophylaxis and/or treatment of pain.

13. The medicament as claimed in claim 8 for prophylaxis and/or treatment of hypotension.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted] 03/06168

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/34 A61K31/197 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 68591 A (HOFFMANN LA ROCHE) 20 September 2001 (2001-09-20) page 2, line 3 -page 3, line 10 examples 1,2,6,7,13-15	1-18
X	AMINO, Y ET AL: "Phenylalanine derivatives enhancing intestinal absorption of insulin in mice" CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 36, no. 11, 1988, pages 4426-4434, XP002257551 PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO., JP ISSN: 0009-2363 examples 12,26,29,13,32,33,34; table II	1-3,8-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2003	10/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	O'Sullivan, P

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C.(Continuation) DOCUMENTS CONSI[redacted]D TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 00 50397 A (TAKAHASHI AKIHIRO ;KATO MASAHIKO (JP); YAMADA SHIGEO (JP); ADACHI) 31 August 2000 (2000-08-31) page 14, line 13 -page 15, line 8 table 3 claim 1	1-18
A	US 4 714 713 A (FUKUSHIMA KOJI ET AL) 22 December 1987 (1987-12-22) claim 1	1-7

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